Assessing the Detection Limit of a Minority Solid-State Form of a Pharmaceutical by ^{1}H Double-Quantum MAS NMR Spectroscopy

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ABSTRACT:

The lower detection limit for two distinct crystalline phases by ^{1}H magic-angle spinning (MAS) solid-state NMR is investigated for a minority amount of cimetidine (anhydrous polymorph A) in a physical mixture with the anhydrous hydrochloride salt of cimetidine. Specifically, two-dimensional ^{1}H double-quantum (DQ) MAS spectra of polymorph A and the anhydrous hydrochloride salt constitute fingerprints for the presence of each of these solid forms. For solid-state NMR data recorded at a ^{1}H Larmor frequency of 850 MHz and a MAS frequency of 30 kHz on ~10 mg of sample, it is shown that, by following the pair of cross peaks at a ^{1}H DQ frequency of 7.4 + 11.6 = 19.0 ppm that are unique to polymorph A, the level of detection for polymorph A in a physical mixture with the anhydrous hydrochloride salt is a concentration of 1% w/w.

Keywords: solid state; NMR; physical characterisation; analytical chemistry; hydrogen bonding; magic-angle spinning, double-quantum

INTRODUCTION

Salt formation is the most general and effective method for improving the aqueous solubility and dissolution rate of acidic and basic drugs. Currently nearly half of all active pharmaceutical ingredients (APIs) used in medication are in salt forms.[1] However, during various processing steps such as milling, compression, drying and granulation, a salt can become unstable chemically and physically, i.e., it may transform to its free acid/base form or into other polymorphs or solvates. Many of the commonly used excipients in tablet formulations are acidic or basic and can, thus, change the local pH of a system. This can affect the stability of the salt and cause the transformation of the salt to the corresponding free acid/base form. The solid-state

transformation from a salt to a free form will alter key properties of the API, such as solubility and dissolution behaviour, leading to undesired changes in the bioavailability of the API.[2] In order to monitor the quality of pharmaceuticals, an effective and highly sensitive quantitation method is required.

A variety of techniques have been used to characterize the physicochemical properties of pharmaceuticals,[3] including powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC) and vibrational spectroscopies, notably infra-red (IR) and Raman. Although PXRD is considered the definitive test for the identification of a specific solid-state form, the effectiveness of PXRD for quantitative analysis of mixtures of solid phases can be diminished when the effects of preferred orientation are significant;[4] however, if the crystal structures of all the solid forms present in the mixture are known, then quantitative analysis can be carried out by Rietveld refinement in which the effects of preferred orientation are taken rigorously into consideration. For example, Li *et al*. have shown[5] that the error associated with distinguishing polymorphs I and II of sulfamerazine by DSC or PXRD was ±3%, which is superior to that achieved by Raman spectroscopy. Siddiqui *et al*. have also used PXRD (and solid-state NMR) to quantify the amount of crystalline tacrolimus solid dispersions,[6,7] while Macfhionnghaile *et al*. have investigated the effect of ball-milling and cryomilling on sulfamerazine using PXRD, IR and near IR spectroscopy.[8] Using terahertz (THz) spectroscopy,[9] Strachan *et al*. have shown that the concentration of carbamazepine form III in a physical mixture with form I can be detected down to a concentration of 1.5%.[10] Moreover, Hisazumi *et al*. have used THz spectroscopy to distinguish between anhydrous and hydrate forms of theophylline with an error of 3% in a pharmaceutical formulation.[11] Recently, Thakral *et al.* have used PXRD to follow salt disproportionation,[12] in which the PXRD data were

measured using a two-dimensional area detector – using this technique, conventional one-dimensional PXRD patterns that are free from the effects of preferred orientation can be obtained by appropriate integration of the two-dimensional data.

Solid-state nuclear magnetic resonance (NMR) spectroscopy is an important method for pharmaceutical analysis.[13-17] While the workhorse method is ^{13}C cross-polarization (CP) magic-angle spinning (MAS), the potential of applying ^{1}H fast MAS NMR is increasingly recognized for solid-state analysis.[18-48] In particular, the ^{1}H double-quantum (DQ) solid-state NMR experiment is a powerful probe of dipolar-coupled protons, with DQ peaks observed for close (typically less than 3.5 Å) through-space H···H proximities.[49-51] Thus, a two-dimensional ^{1}H DQ spectrum represents a "fingerprint" for a specific three-dimensional packing arrangement adopted by an organic molecule, emphasising the advantage over one-dimensional ^{1}H or ^{13}C spectra of spreading out into two dimensions. In this way, by using a high-resolution ^{1}H DQ CRAMPS (combined rotation and multiple-pulse spectroscopy) approach,[52] it has been shown how the presence of only the anhydrous form and not a hydrate form of an API in tablet formulation can be established.[19] Due to the spectral noise associated with the application of ^{1}H homonuclear decoupling in the CRAMPS approach, it is only possible to conclude that the hydrate form is absent within a detection limit of ~5% for the spectra presented in Ref.[19]. An alternative approach is to use a combination of fast MAS and high magnetic field to give ^{1}H DQ MAS spectra, where the resolution, while not as good as with the ^{1}H DQ CRAMPS method,[51] is sufficient to resolve distinct spectral features. For the specific case of the anhydrous hydrochloride salt of cimetidine (the crystal structure of which has been determined recently[53] by a combined PXRD and NMR crystallography strategy) and the free form of cimetidine (anhydrous polymorph A), this paper investigates the

lower limit of detection of a minority solid-state form of an API, present in a physical mixture with another crystalline phase of the same API, using ^{1}H DQ MAS NMR spectroscopy.

EXPERIMENTAL SECTION

Cimetidine and cimetidine hydrochloride were purchased from Sigma-Aldrich and used without further purification. The identification of the specific solid-state form was confirmed by powder X-ray diffraction as shown in Refs.[33,53]. Samples containing 10%, 5%, 1% and 0.5% w/w polymorph A / anhydrous HCl salt were prepared by physically mixing appropriately weighed quantities of the two pure solid phases.

Solid-state NMR experiments were performed on a Bruker Avance III spectrometer operating at a ^{1}H Larmor frequency of 850.2 MHz (B_0 = 20.0 T) using a Bruker triple-resonance probe, operating in double-resonance mode, supporting rotors of 2.5 mm outer diameter (corresponding to ~10 mg of sample). A MAS frequency of 30 kHz was used. The pulse sequence and coherence transfer pathway diagram for the ^{1}H DQ MAS[49] experiment using BABA (back-to-back) recoupling[54,55] experiment are shown in Figure 7 of Ref.[56]. A 16-step phase cycle was used to select $\Delta p = \pm 2$ on the DQ excitation block and $\Delta p = -1$ on the final 90° pulse, where p is the coherence order. The ^{1}H 90° pulse length was 2.5 μs. In all experiments, 160 t_1 FIDs were recorded with a rotor-synchronized t_1 increment of 33.3 μs using the States-TPPI (time-proportional phase incrementation) method to achieve sign discrimination in F_1. For the anhydrous HCl salt of cimetidine and polymorph A of cimetidine, 16 transients were co-added with a recycle delay of 3 s. For the physical mixtures of polymorph A and the anhydrous HCl salt, a recycle delay of 9 s was used and 16

(10% and 5% w/w mixture samples), 48 (1% w/w mixture sample) and 112 transients (0.5% w/w mixture sample) were co-added. The experimental times were thus 2 hours (anhydrous cimetidine hydrochloride and cimetidine polymorph A), 6 hours (10% and 5% w/w mixture samples), 19 hours (1% w/w mixture sample) and 44 hours (0.5% w/w mixture sample).

^{1}H chemical shifts are referenced with respect to neat TMS using adamantane as a secondary reference (1.85 ppm for ^{1}H).[57] Experimental ^{1}H chemical shifts are stated to an accuracy of ±0.1 ppm.

RESULTS AND DISCUSSION

^{1}H DQ MAS Solid-State NMR Spectra

In previous studies, ^{13}C CP MAS one-dimensional spectra, as well as the results of various heteronuclear dipolar experiments, have been presented for a free form of cimetidine (polymorph A),[58,59] while a ^{13}C CP MAS spectrum of the anhydrous HCl salt of cimetidine as well as a GIPAW (gauge-including projector-augmented wave) calculation[60,61] of the NMR parameters (for the reported crystal structure[53] following geometry optimization) have been presented recently. Tatton *et al.* have also presented ^{15}N-^{1}H spectral-editing and ^{14}N-^{1}H and ^{15}N-^{1}H correlation spectra for polymorph A of cimetidine, together with GIPAW calculations of the chemical shielding and electric field gradient tensors for the reported crystal structure[62] following geometry optimization.[33] Note that distances stated in this paper are from the geometry-optimized crystal structures on which these GIPAW calculations were carried out (available as Supporting Information with Refs. [33,53]).

Fig. 1a and 1b present ^{1}H DQ MAS NMR spectra of (a) the anhydrous HCl salt of cimetidine and (b) polymorph A of cimetidine, recorded at a ^{1}H Larmor

frequency of 850 MHz and a MAS frequency of 30 kHz. Since ^{1}H linewidths for the strongly dipolar-coupled network of protons in organic solids decrease with increasing MAS frequency,[63,64] narrower ^{1}H linewidths would be observed using the higher MAS frequencies of >60 kHz that can be achieved with rotors of smaller outer diameter (1.3 mm and less). However, the improved resolution would come at the cost of lower sensitivity associated with the considerably reduced sample volume (corresponding to sample mass ~1 mg or less). Enhanced resolution could also be achieved using the ^{1}H DQ CRAMPS approach (e.g., see Fig. 3 of Ref.[51]) but, as noted in the Introduction, the disadvantage of using ^{1}H homonuclear decoupling is the observation of additional "noise" in the spectra which limits the lower detection of the minority phase to ~5%. For these reasons, it was decided that 30 kHz MAS at a ^{1}H Larmor frequency of 850 MHz provided the best compromise of sufficiently high-resolution and optimum sensitivity for ^{1}H DQ MAS NMR spectroscopy of the anhydrous HCl salt and polymorph A of cimetidine – see the spectra presented in Fig. 1a and 1b.

The ^{1}H DQ MAS NMR spectra presented in Fig. 1 were recorded using one rotor period of BABA recoupling.[54,55] Such ^{1}H DQ MAS NMR spectra probe DQ coherences between pairs of through-space dipolar coupled protons corresponding to a close (typically less than 3.5 Å) H···H distance,[49,51] with DQ peaks observed at the sum of the two single-quantum (SQ) frequencies. Table 1 presents an assignment of the experimentally observed ^{1}H chemical shifts for polymorph A and the anhydrous HCl salt of cimetidine based on GIPAW calculations (as reported previously[33,53]). The significant change in the ^{1}H chemical shift of H3 reflects the change from an NH···N

intermolecular hydrogen bond with N12 as the acceptor in polymorph A (involving uncharged donor and acceptor groups) to an $NH^+\cdots Cl^-$ intermolecular hydrogen bond (involving charged donor and acceptor groups) in the anhydrous HCl salt.

Tables 2 and 3 list H···H proximities under 3.5 Å for the NH and imidazole CH protons and the corresponding ^{1}H DQ shifts for the anhydrous HCl salt and polymorph A of cimetidine, respectively. For the anhydrous HCl salt, the NH^+ (H1) and NH (H3) imidazole ^{1}H chemical shifts overlap (at 15.0 ppm, see Table 1). Thus, in the ^{1}H DQ MAS spectrum in Fig. 1a, the pair of ^{1}H DQ peaks at δ_{DQ} = 15.0 + 9.4 = 24.4 ppm corresponds to an intramolecular proximity of 2.57 Å for the imidazole CH (H2) with both the NH^+ (H1) and NH (H3) protons – see Table 2. We also note the very weak diagonal peak at δ_{DQ} = 15.0 + 15.0 = 30.0 ppm in Fig. 1a that corresponds to a 3.43 Å intermolecular proximity of the NH^+ (H1) and NH (H3) protons (also see Table 2). As described in Ref. [65], to a first approximation, the relative intensity of distinct ^{1}H DQ peaks at the same ^{1}H single-quantum chemical shift is proportional to the ratio of the square of the dipolar coupling constants and hence is inversely proportional to ratio of H···H distances to the sixth power – note that $(3.43/2.57)^6$ = 5.7. Other cross peaks observed for the NH groups in the ^{1}H DQ MAS spectra in Fig. 1a and 1b are due to intra- and intermolecular proximities to CH_2 and CH_3 protons (see Tables 2 and 3).

This study is focused on the pair of ^{1}H DQ peaks due to the intramolecular proximity of 2.57 and 2.55 Å for the imidazole H2 (CH) and H3 (NH) protons, whereby δ_{DQ} = 15.0 + 9.4 = 24.4 ppm in Fig. 1a for the anhydrous HCl salt and δ_{DQ} = 11.6 + 7.4 = 19.0 ppm in Fig. 1b for polymorph A. The evident change in the positions of the pair of ^{1}H DQ peaks due to the intramolecular proximity of the

imidazole H2 (CH) and H3 (NH) protons between the anhydrous HCl salt and polymorph A constitutes a "fingerprint" that is a diagnostic for the presence of either or both of the distinct solid-state forms.

Probing the Level of Detection of a Minority Phase in a Physical Mixture of Two Distinct Crystalline Phases

To determine the level of detection by ^{1}H DQ MAS NMR of polymorph A of cimetidine in a physical mixture with the anhydrous HCl salt of cimetidine, spectra were recorded for samples comprising 10%, 5%, 1% and 0.5% w/w mixtures of polymorph A / anhydrous HCl salt. Specifically, Fig. 1c presents a ^{1}H DQ MAS NMR spectrum of the 10% w/w mixture (note the lower base contour in Fig. 1c as compared to Fig. 1a and 1b). It is evident that a weak pair of ^{1}H DQ peaks at δ_{DQ} = 11.6 + 7.4 = 19.0 ppm due to polymorph A is observed in addition to the stronger ^{1}H DQ peaks at δ_{DQ} = 15.0 + 9.4 = 24.4 ppm due to the anhydrous HCl salt. Thus, it is necessary to focus on the peaks observed at a ^{1}H DQ frequency of 19.0 ppm, and Fig. 2 presents slices at this DQ frequency for (a) the anhydrous HCl salt of cimetidine, (b) polymorph A of cimetidine, and (c-f) physical mixtures of polymorph A with the anhydrous HCl salt with (c) 10%, (d) 5%, (e) 1%, and (f) 0.5% w/w of polymorph A. For the anhydrous HCl salt, we note that there are ^{1}H DQ peaks at δ_{DQ} = 15.0 + 4.0 = 19.0 ppm due to proximity with aliphatic protons – see Figs. 1a and 2a. The spreading into two dimensions allows these to be distinguished from the ^{1}H DQ peaks at δ_{DQ} = 11.6 + 7.4 = 19.0 ppm, characteristic of polymorph A. Following the dashed lines through the peaks at δ_{SQ} = 11.6 and 7.4 ppm, it is evident that the ^{1}H DQ peaks due to polymorph A are still evident above the noise level down to the 1% w/w mixture in Fig. 2e. This conclusion is confirmed by the signal to noise analysis presented in

Table 4 for the peaks at a ^{1}H DQ frequency of 19.0 ppm for the H2 and H3 ^{1}H SQ resonances at 11.6 and 7.4 ppm. Following the guidance of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Validation of Analytical Procedures: Text and Methodology Q2(R1), section 6.2 states that "A signal-to-noise ratio between 3 or 2:1 is generally considered acceptable for estimating the detection limit".[66] As such, the data in Table 4 establishes 1% w/w as the level of detection using ^{1}H DQ MAS NMR at 30 kHz MAS and a ^{1}H Larmor frequency of 850 MHz for two crystalline phases of cimetidine.

CONCLUSIONS

Two distinct crystalline phases of cimetidine, polymorph A and the anhydrous HCl salt, are clearly distinguished using ^{1}H DQ MAS solid-state NMR spectroscopy by focusing on the pair of ^{1}H DQ peaks due to the intramolecular proximity (2.55 or 2.57 Å) of the neighbouring H2 (CH) and H3 (NH) protons of the imidazole ring. Protonation at the N1 site in the anhydrous HCl salt as well as the fact that the two distinct solid-state forms have different intermolecular hydrogen-bonding arrangements leads to ^{1}H DQ peaks at δ_{DQ} = 15.0 + 9.4 = 24.4 ppm for the anhydrous HCl salt and at δ_{DQ} = 11.6 + 7.4 = 19.0 ppm for polymorph A. By spreading out the peaks into two dimensions, the observation of ^{1}H DQ peaks at δ_{DQ} = 11.6 + 7.4 = 19.0 ppm is an unambiguous indicator of the presence of polymorph A. Using this "fingerprint", solid-state NMR experiments carried out at a ^{1}H Larmor frequency of 850 MHz and a MAS frequency of 30 kHz have shown that polymorph A can be

detected and quantified in a physical mixture with the anhydrous HCl salt down to a concentration of 1% w/w. Considering literature reports (see Introduction), this level of detection matches and in some cases improves upon that reported for other analytical techniques, e.g., PXRD, DSC, Raman spectroscopy and THz spectroscopy. In particular, we emphasize that distinguishing between two crystalline phases represents a different challenge to the identification of a minority amount of a crystalline phase in the presence of an amorphous phase.

We note that employing ^{1}H DQ MAS represents a complementary approach to solid-state NMR of other nuclei, notably ^{13}C and ^{19}F.[67,68] Moreover, it has recently been shown that the sensitivity of solid-state NMR spectroscopy of moderately sized organic molecules can be significantly enhanced (e.g., by 5 times for paracetamol) by employing dynamic nuclear polarization (DNP), such that ^{13}C refocused INADEQUATE spectra can be recorded at natural isotopic abundance in 16 hours for sulfathiazole (which has a long T_1 relaxation time, necessitating a recycle delay of 30 s)[69] and ^{15}N-^{1}H correlation spectra can be obtained also at natural isotopic abundance for a pharmaceutical formulation.[70] With the recent development of new DNP 1.3 mm MAS probe technology that allows faster MAS,[71] this approach seems promising for progressing to even lower levels of detection of minority solid-state forms by ^{1}H DQ MAS. This approach would also reduce the required experimental time (in this work, 19 hours for the two-dimensional spectrum of the 1% w/w sample), noting that experimental times are typically shorter for other techniques such as PXRD, Raman and IR. Finally, as shown in our earlier work employing a ^{1}H DQ CRAMPS approach,[19] we note that the ^{1}H DQ solid-state NMR method presented here is readily applicable to tablet formulations with the shift of ^{1}H DQ peaks due to hydrogen-

bonded protons to high ppm helping to avoid overlap with ^{1}H resonances of the excipients.

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Figure Captions

Figure 1. ^{1}H (850 MHz) DQ MAS (30 kHz) spectra of (a) the anhydrous HCl salt of cimetidine, (b) polymorph A of cimetidine, and (c) a 10% w/w physical mixture of polymorph A with the anhydrous HCl salt. An assignment of the ^{1}H chemical shifts is presented in Table 1, while Tables 2 and 3 list the expected ^{1}H DQ peaks based on H-H proximities extracted from the geometry-optimized (CASTEP) crystal structures. The thick horizontal lines in (a) and (b) denote the pair of ^{1}H DQ peaks corresponding to the intramolecular proximity of the imidazole H2 (CH) and H3 (NH) protons, noting that for the anhydrous HCl salt this overlaps with the pair of ^{1}H DQ peaks corresponding to the intramolecular proximity of the imidazole H2 (CH) and H1 (NH^{+}) protons. The base contour levels are at (a) 5.4%, (b) 11% and (c) 2.6% with respect to the maximum peak height. (Note that a conference abstract has presented the spectra in this figure in a different format.[72])

Figure 2. Slices corresponding to a ^{1}H DQ frequency of 19.0 ppm, as extracted from two-dimensional ^{1}H (850 MHz) DQ MAS (30 kHz) spectra of (a) the anhydrous HCl salt of cimetidine, (b) polymorph A of cimetidine, and (c-f) physical mixtures of polymorph A with the anhydrous HCl salt with (c) 10%, (d) 5%, (e) 1%, and (f) 0.5% w/w of polymorph A.

Tables

Table 1. Experimental[a] and GIPAW calculated[b] ^{1}H chemical shifts (in ppm) for the anhydrous HCl salt and polymorph A of cimetidine

atom label	atom descriptor	anhydrous HCl salt		polymorph A	
		expt.	calc.	expt.	calc.
H1	NH^{+}	15.0	15.5	–	–
H2	CH	9.4	9.2	7.4	7.1
H3	NH	15.0	15.3	11.6	11.9
H6a	CH_2	3.6	4.3	4.0	3.4
H6b	CH_2	3.6	3.8	4.0	3.0
H7a-c[c]	CH_3	2.6	2.9	2.0	1.3
H8a	CH_2	2.6	2.4	3.0	1.3
H8b	CH_2	2.6	0.7	3.0	0.2
H9a	CH_2	2.6	2.8	3.0	2.4
H9b	CH_2	2.6	1.9	3.0	2.7
H10	NH	5.0	4.6	8.2	8.2
H15	NH	6.7	6.9	9.7	9.6
H16a-c[c]	CH_3	2.6	1.4	2.0	1.5

[a] It is not possible to distinguish separate CH_2 and CH_3 ^{1}H resonances in the experimental spectra.

[b] Calculated isotropic chemical shifts are obtained from the calculated absolute shielding as $\delta_{iso}^{calc} = \sigma_{ref} - \sigma_{cal}$, where $\sigma_{ref} = 30.0$ ppm.

[c] For CH_3 groups, the stated value of the calculated isotropic chemical shift is the average for the three protons.

Table 2. H···H proximities[a] (< 3.5 Å) and corresponding ^{1}H DQ shifts (see Fig. 1a) for the NH and imidazole CH protons in the anhydrous HCl salt of cimetidine.

	Atom label	δ_{SQ} / ppm	δ_{DQ} / ppm	distance / Å
H1 (NH^+)	H2 (CH)	9.4	24.4	2.57
(15.0 ppm)	H6b (CH_2)	3.6	18.6	2.70
	H7c (CH_3)	*2.6*	*17.6*	*2.82*
	H16c (CH_3)	*2.6*	*17.6*	*2.94*
	H16a (CH_3)	*2.6*	*17.6*	*3.18*
	H3 (NH)	*15.0*	*30.0*	*3.43*
	H7a (CH_3)	*2.6*	*17.6*	*3.49*
H2 (CH)	H1 (NH+)	15.0	24.4	2.57
(9.4 ppm)	H3 (CH)	15.0	24.4	2.57
	H7c (CH_3)	*2.6*	*12.0*	*2.69*
	H6b (CH_2)	*3.6*	*13.0*	*2.82*
	H6a (CH_2)	*3.6*	*13.0*	*3.06*
	H6a (CH_2)	*3.6*	*13.0*	*3.13*
	H16b (CH_3)	*2.6*	*12.0*	*3.39*
H3 (NH)	*H2 (CH)*	*9.4*	*24.4*	*2.57*
(15.0 ppm)	H6b (CH_2)	3.6	18.6	2.71
	H7c (CH_3)	*2.6*	*17.6*	*2.73*
	H6a (CH_2)	3.6	18.6	2.95
	H7b (CH3)	*2.6*	*17.6*	*3.04*
	H9a (CH_2)	*2.6*	*17.6*	*3.15*
	H16c (CH_3)	*2.6*	*17.6*	*3.35*

	H6a (CH_2)	*3.6*	*18.6*	*3.39*
	H1 (NH^+)	*15.0*	*30.0*	*3.43*
H10 (NH)	H9a (CH_2)	2.6	7.6	2.29
(5.0 ppm)	H9b (CH_2)	2.6	7.6	2.94
	H8b (CH_2)	2.6	7.6	2.98
	H7b (CH_3)	2.6	7.6	3.03
	H16c (CH_3)	*2.6*	*7.6*	*3.31*
	H8a (CH_2)	2.6	7.6	3.33
	H7a (CH_3)	2.6	7.6	3.36
H15 (NH)	H9b (CH_2)	2.6	9.3	2.17
(6.7 ppm)	H16a (CH_3)	2.6	9.3	2.24
	H8a (CH_2)	2.6	9.3	2.26
	H16b (CH_3)	2.6	9.3	2.72
	H16c (CH_3)	2.6	9.3	2.93
	H8a (CH_2)	*2.6*	*9.3*	*2.94*

[a] Distances are stated for the geometry-optimized (CASTEP) crystal structure. Intermolecular proximities are in italics.

Table 3. H···H proximities[a] (< 3.5 Å) and corresponding ^{1}H DQ shifts (see Fig. 1b) for the NH and imidazole CH protons in the geometry-optimized (CASTEP) crystal structure of polymorph A of cimetidine.

	Atom label	δ_{SQ} / ppm	δ_{DQ} / ppm	distance / Å
H2 (CH)	H3 (NH)	11.6	19.0	2.55
(7.4 ppm)	H16a (CH_3)	2.0	9.4	2.59
	H7c (CH_3)	*2.0*	*9.4*	*2.87*
	H7a (CH_3)	*2.0*	*9.4*	*2.93*
	H15 (NH)	9.7	17.1	3.00
	H7b (CH_3)	*2.0*	*9.4*	*3.05*
	H6b (CH_2)	*4.0*	*11.4*	*3.27*
	H16c (CH_3)	*2.0*	*9.4*	*3.50*
H3 (NH)	*H16b (CH_3)*	*2.0*	*13.6*	*2.52*
(11.6 ppm)	H2 (CH)	7.4	19.0	2.55
	H7a (CH_3)	*2.0*	*13.6*	*2.59*
	H7b (CH_3)	*2.0*	*13.6*	2.81
	H7c (CH_3)	2.0	13.6	3.09
	H7b (CH_3)	*2.0*	*13.6*	*3.10*
	H16a (CH_3)	*2.0*	*13.6*	*3.13*
H10 (NH)	H9a (CH_2)	3.0	11.2	2.27
(8.2 ppm)	*H16c (CH_3)*	*2.0*	*10.2*	*2.71*
	H9b (CH_2)	3.0	11.2	2.93
	H8b (CH_2)	3.0	11.2	2.99

	H8a (CH_2)	3.0	11.2	3.42
H15 (NH)	H9b (CH_2)	3.0	12.7	2.20
(9.7 ppm)	H16a (CH_3)	2.0	11.7	2.22
	H8a (CH_2)	3.0	12.7	2.29
	H16c (CH_3)	2.0	11.7	2.81
	H16b (CH_3)	2.0	11.7	2.90
	H2 (CH)	7.4	16.1	3.00
	H6a (CH_2)	4.0	13.7	3.19
	H7b (CH_3)	*2.0*	*11.7*	*3.22*
	H7c (CH_3)	*2.0*	*11.7*	*3.40*

[a] Distances are stated for the geometry-optimized (CASTEP) crystal structure. Intermolecular proximities are in italics.

Table 4. Signal to noise ratios for the peaks at a ^{1}H DQ frequency of 19.0 ppm for the ^{1}H SQ H2 and H3 resonances at 11.6 and 7.4 ppm (see Figure 2) for physical mixtures of polymorph A with the anhydrous HCl salt.

w/w of polymorph A	H2	H3
10%	16.6	16.2
5%	6.3	7.0
1%	3.3	2.4
0.5%	1.6	1.0